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NOV 12, 2003 Monica Eutsler
Date Name

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 01-1693-F)
(previously 13615.21USU1)

In re Application of:	
Fang et al.	
Serial No.: 09/895,871	Before the Examiner: Richard L. Raymond
Filed: June 29, 2001	Art Unit: 1624
For: Compounds to Treat Alzheimer's Disease	Confirmation No.: 5372

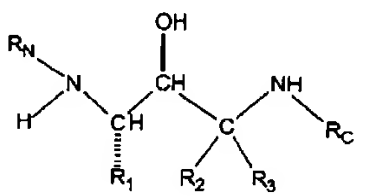
RESPONSE TO THE OFFICE ACTION
MAILED JUNE12, 2003

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Responsive to the Office Action mailed January 13, 2003, Applicants respectfully request the Examiner to reconsider the above-identified patent application in view of the following Amendments and Remarks.

1. (Currently Amended) A substituted amine of formula (X)



(X)

where R_1 is:

~~(I) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkyl (optionally substituted with C_1-C_3 alkyl and C_1-C_3 alkoxy), F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are H or C_1-C_6 alkyl, and OC=O $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are as defined above,~~

~~(II) CH_2-S(O)$_{0-2}$-(C_1-C_6 alkyl),~~

~~(III) CH_2-CH_2-S(O)$_{0-2}$-(C_1-C_6 alkyl),~~

~~(IV) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are H or C_1-C_6 alkyl,~~

~~(V) C_2-C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are H or C_1-C_6 alkyl,~~

(VI) $-(CH_2)_{n1}-(R_{1\text{-aryl}})$ where n_1 is ~~zero or~~ one and where $R_{1\text{-aryl}}$ is phenyl, ~~1-naphthyl, 2-naphthyl and indanyl, indenyl,~~

~~dihydronaphthayl, or tetralinyl~~ optionally substituted with one, two, three or four of the following substituents on the aryl ring:

(A) C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(B) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are -H or C_1-C_6 alkyl,

(C) C_2-C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are -H or C_1-C_6 alkyl,

(D) -F, Cl, -Br, or -I,

(E) $-C_1$-C_6 alkoxy optionally substituted with one, two, or three -F,

(F) $-NR_{N\text{-}2}R_{N\text{-}3}$ where $R_{N\text{-}2}$ and $R_{N\text{-}3}$ are as defined below,

(G) -OH,

(H) -C≡N,

(I) C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are -H or C_1-C_6 alkyl,

(J) $-CO-(C_1$-C_4 alkyl),

(K) $-SO_2-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(L) $-CO-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, or

(M) $-SO_2-(C_1-C_4$ alkyl),

~~(VII) $-(CH_2)_{n1}-(R_{1\text{ heteroaryl}})$ where n_1 is as defined above and where $R_{1\text{ heteroaryl}}$ is selected from the group consisting of:~~

~~pyridinyl,~~

~~pyrimidinyl,~~

~~quinolinyl,~~

~~benzothienyl,~~

~~indolyl,~~

~~indolinyl,~~

~~pryidazinyl,~~

~~pyrazinyl,~~

~~isoindolyl,~~

~~isoquinolyl,~~

~~quinazolinyl,~~

~~quinoxalinyl,~~

~~phthalazinyl,~~

~~imidazolyl,~~

~~isoxazolyl,~~

~~pyrazolyl,~~

~~oxazolyl,~~

~~thiazolyl,~~

~~indolizinyl,~~

~~indazolyl,~~

~~benzothiazolyl,~~

~~benzimidazolyl,~~

~~benzofuranyl,~~

~~furanyl,~~

~~thienyl,~~

~~pyrrolyl,~~

~~oxadiazolyl,~~

~~thiadiazolyl,~~
~~triazolyl,~~
~~tetrazolyl,~~
~~oxazolopyridinyl,~~
~~imidazopyridinyl,~~
~~isothiazolyl,~~
~~naphthyridinyl,~~
~~cinnolinyl,~~
~~carbazolyl,~~
~~beta-carbolinyl,~~
~~isochromanyl,~~
~~chromanyl,~~
~~tetrahydroisoquinolinyl,~~
~~isoindolinyl,~~
~~isobenzotetrahydrofuranyl,~~
~~isobenzotetrahydrothienyl,~~
~~isobenzothienyl,~~
~~benzoxazolyl,~~
~~pyridopyridinyl,~~
~~benzotetrahydrofuranyl,~~
~~benzotetrahydrothienyl,~~
~~purinyl,~~
~~benzodioxolyl,~~
~~triazinyl,~~
~~phenoxazinyl,~~
~~phenothiazinyl,~~
~~pteridinyl,~~
~~benzothiazolyl,~~
~~imidazopyridinyl,~~
~~imidazothiazolyl,~~
~~dihydrobenzisoxazinyl,~~
~~benzisoxazinyl,~~

~~benzoxazinyl,~~
~~dihydrobenzisothiazinyl,~~
~~benzopyranyl,~~
~~benzothiopyranyl,~~
~~coumarinyl,~~
~~isocoumarinyl,~~
~~chromonyl,~~
~~chromanonyl,~~
~~pyridinyl N-oxide~~
~~tetrahydroquinolinyl~~
~~dihydroquinolinyl~~
~~dihydroquinolinonyl~~
~~dihydroisoquinolinonyl~~
~~dihydrocoumarinyl~~
~~dihydroisocoumarinyl~~
~~isoindolinonyl~~
~~benzodioxanyl~~
~~benzoxazolinonyl~~
~~pyrrolyl N-oxide,~~
~~pyrimidinyl N-oxide,~~
~~pyridazinyl N-oxide,~~
~~pyrazinyl N-oxide,~~
~~quinolinyl N-oxide,~~
~~indolyl N-oxide,~~
~~indolinyl N-oxide,~~
~~isoquinolyl N-oxide,~~
~~quinazolinyl N-oxide,~~
~~quinoxalinyl N-oxide,~~
~~phthalazinyl N-oxide,~~
~~imidazolyl N-oxide,~~
~~isoxazolyl N-oxide,~~
~~oxazolyl N-oxide,~~

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thiazolyl N-oxide,
indolizinyl N-oxide,
indazolyl N-oxide,
benzothiazolyl N-oxide,
benzimidazolyl N-oxide,
pyrrolyl N-oxide,
oxadiazolyl N-oxide,
thiadiazolyl N-oxide,
triazolyl N-oxide,
tetrazolyl N-oxide,
benzothiopyranyl S-oxide, and
benzothiopyranyl S,S-dioxide,

where the $R_{1\text{-heteroaryl}}$ group is bonded to $(CH_2)_{n1}$ by any ring atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three or four of:

(1) C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, F, Cl, Br, I, -OH, -CH, C=N, CF_3, C_1-C_3 alkoxy, and $NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(2) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, -CH, C=N, CF_3, C_1-C_3 alkoxy, and $NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are -H or C_1-C_6 alkyl,

(3) C_2-C_6 alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, -SH, -C=N,

~~CF_3, C_1-C_3 alkoxy, and $-NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are H or C_1-C_6 alkyl,~~

~~(4) F, Cl, Br, or I,~~

~~(5) C_1-C_6 alkoxy optionally substituted with one, two, or three F,~~

~~(6) $NR_{N3}R_{N3}$ where R_{N3} and R_{N3} are as defined below,~~

~~(7) OH,~~

~~(8) C≡N,~~

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~~(9) C_3-C_8 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of -F, Cl, OH, SH, -C≡N, CF_3, C_1-C_3 alkoxy, and $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are H or C_1-C_6 alkyl,~~

~~(10) CO (C_1-C_4 alkyl),~~

~~(11) $SO_2NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are as defined above,~~

~~(12) $CONR_{1a}R_{1b}$ where R_{1a} and R_{1b} are as defined above,~~

~~(13) SO_2 (C_1-C_4 alkyl), with the proviso that when n_1 is zero $R_{1\ heteroaryl}$ is not bonded to the carbon chain by nitrogen,~~

~~(VIII) $(CH_2)_{n1}$ ($R_{1\ heterocycle}$) where n_1 is as defined above and $R_{1\ heterocycle}$ is selected from the group consisting of:~~

~~morpholinyl,~~

~~thiomorpholinyl,~~

~~thiomorpholinyl S oxide,~~

~~thiomorpholinyl S,S dioxide,~~

~~piperazinyl,~~

~~homopiperazinyl,~~

~~pyrrolidinyl,~~

~~pyrrolinyl,~~

tetrahydropyranyl,
piperidinyl,
tetrahydrofuranyl,
tetrahydrothienyl,
homopiperidinyl,
homomorpholinyl,
homothiomorpholinyl,
homothiomorpholinyl S,S-dioxide,
oxazolidinonyl,
dihydropyrazolyl,
dihydropyrrolyl,
dihydropyrazinyl,
dihydropyridinyl,
dihydropyrimidinyl,
dihydrofuryl,
dihydropyranyl,
tetrahydrothienyl S oxide,
tetrahydrothienyl S,S-dioxide, and
homothiomorpholinyl S oxide,

where the $R_{1\text{ heterocycle}}$ group is bonded by any atom of the parent $R_{1\text{ heterocycle}}$ group substituted by hydrogen such that the new bond to the $R_{1\text{ heterocycle}}$ group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:

(1) C_1-C_6 alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $NR_{1a}R_{1b}$ where R_{1a} and R_{1b} are as defined above,

(2) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three

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~~substituents selected from the group consisting of F, Cl, OH, SH, C=N, CF_3, C_1-C_3-alkoxy, and $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are H or C_1-C_6-alkyl,~~

~~(3) C_2-C_6-alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, SH, C=N, CF_3, C_1-C_3-alkoxy, and $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are H or C_1-C_6-alkyl,~~

~~(4) F, Cl, Br, or I,~~

~~(5) C_1-C_6-alkoxy optionally substituted with one, two, or three F,~~

~~(6) $NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined below,~~

~~(7) OH,~~

~~(8) C=N,~~

~~(9) C_3-C_7-cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of F, Cl, OH, SH C=N, CF_3, C_1-C_3-alkoxy, and $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are H or C_1-C_6-alkyl,~~

~~(10) CO (C_1-C_4-alkyl),~~

~~(11) $SO_2NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,~~

~~(12) $CONR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,~~

~~(13) SO_2 (C_1-C_4-alkyl),~~

~~(14) =O, with the proviso that when n_2 is zero $R_{1\text{-heterocycle}}$ is not bonded to the carbon chain by nitrogen;~~

where R_2 is:

(I) -H, or

(II) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above;

where R_3 is:

(I) -H, or

(II) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above;

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and where R_2 and R_3 are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six, or seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, $-SO_2-$, and $-NR_{N-2}-$, where R_{N-2} is as defined below;

where R_N is:

(I) R_{N-1}-X_N- where X_N is ~~selected from the group consisting of:~~

~~(A) -CO-, and~~

~~(B) $-SO_2-$~~

where R_{N-1} is selected from the group consisting of:

~~(A) $R_{N\text{-}aryl}$ where $R_{N\text{-}aryl}$ is~~ phenyl, ~~1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl,~~ optionally substituted with one, two or three of the following substituents which can be the same or different and are:

(1) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(2) -OH,

(3) $-NO_2$,

(4) -F, -Cl, -Br, or -I,

(5) -CO-OH,

(6) -C≡N,

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(7) $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are selected from the group consisting of:

(a) -H,

(b) -C_1-C_6 alkyl optionally substituted with one ~~substitutent~~ substituent selected from the group consisting of:

(i) -OH, and

(ii) $-NH_2$,

(c) -C_1-C_6 alkyl optionally substituted with one to three -F, -Cl, -Br, or -I,

(d) -C_3-C_7 cycloalkyl,

(e) -(C_1-C_2 alkyl)-(C_3-C_7 cycloalkyl),

(f) -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),

(g) -C_2-C_6 alkenyl with one or two double bonds,

(h) -C_2-C_6 alkynyl with one or two triple bonds,

(i) -C_1-C_6 alkyl chain with one double bond and one triple bond,

(j) $-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above, and

(k) $-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(8) $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl),

(9) $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl with one, two or three double bonds),

(10) $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl with one, two or three triple bonds),

(11) $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl),

(12) $-(CH_2)_{0-4}-CO-R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above,

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(13) $-(CH_2)_{0-4}-CO-R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(14) $-(CH_2)_{0-4}-CO-R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(15) $-(CH_2)_{0-4}-CO-R_{N-4}$ where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,

(16) $-(CH_2)_{0-4}-CO-O-R_{N-5}$ where R_{N-5} is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) $-(CH_2)_{0-2}-(R_{1\text{-aryl}})$ where $R_{1\text{-aryl}}$ is as defined above,

(c) C_2-C_6 alkenyl containing one or two double bonds,

(d) C_2-C_6 alkynyl containing one or two triple bonds,

(e) C_3-C_7 cycloalkyl,

(f) $-(CH_2)_{0-2}-(R_{1\text{-heteroaryl}})$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(17) $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(18) $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl),

(19) $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl),

(20) $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl),

(21) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-O-R_{N-5}$ where R_{N-5} can be the same or different and is as defined above,

(22) $-(CH_2)_{0-4}-N(H$ or $R_{N-5})-CO-N(R_{N-5})_2$, where R_{N-5} can be the same or different and is as defined above,

(23) $-(CH_2)_{0-4}-N-CS-N(R_{N-5})_2$, where R_{N-5} can be the same or different and is as defined above,

(24) $-(CH_2)_{0-4}-N(-H$ or $R_{N-5})-CO-R_{N-2}$ where R_{N-5} and R_{N-2} can be the same or different and are as defined above,

(25) $-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(26) $-(CH_2)_{0-4}-R_{N-4}$ where R_{N-4} is as defined above,

(27) $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl),

(28) $-(CH_2)_{0-4}-O-P(O)-(OR_{N\text{-aryl-1}})_2$ where $R_{N\text{-aryl-1}}$ is -H or C_1-C_4 alkyl,

(29) $-(CH_2)_{0-4}-O-CO-N(R_{N-5})_2$ where R_{N-5} is as defined above,

(30) $-(CH_2)_{0-4}-O-CS-N(R_{N-5})_2$ where R_{N-5} is as defined above,

(31) $-(CH_2)_{0-4}-O-(R_{N-5})_2$ where R_{N-5} is as defined above,

(32) $-(CH_2)_{0-4}-O-(R_{N-5})_2-COOH$ where R_{N-5} is as defined above,

(33) $-(CH_2)_{0-4}-S-(R_{N-5})_2$ where R_{N-5} is as defined above,

(34) $-(CH_2)_{0-4}-O-$ (C_1-C_6 alkyl optionally substituted with one, two, three, four, or five -F),

(35) C_3-C_7 cycloalkyl,

(36) C_2-C_6 alkenyl with one or two double bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(37) C_2-C_6 alkynyl with one or two triple bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, $-NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

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(38) $-(CH_2)_{0-4}-N(-H$ or $R_{N-5})-SO_2-R_{N-2}$ where R_{N-5} and R_{N-2} can be the same or different and are as described above, or

(39) $-(CH_2)_{0-4}-$ C_3-C_7 cycloalkyl,

~~(B) $R_{N\text{-heteroaryl}}$ where $R_{N\text{-heteroaryl}}$ is selected from the group consisting of:~~

~~pyridinyl,~~
~~pyrimidinyl,~~
~~quinolinyl,~~
~~benzothienyl,~~
~~indolyl,~~
~~indolinyl,~~
~~pryidazinyl,~~
~~pyrazinyl,~~
~~isoindolyl,~~
~~isoquinolyl,~~
~~quinazolinyl,~~
~~quinoxalinyl,~~
~~phthalazinyl,~~
~~imidazolyl,~~

~~-isoxazolyl,~~
~~-pyrazolyl,~~
~~-oxazolyl,~~
~~-thiazolyl,~~
~~-indolizinyl,~~
~~-indazolyl,~~
~~-benzothiazolyl,~~
~~-benzimidazolyl,~~
~~-benzofuranyl,~~
~~-furanyl,~~
~~-thienyl,~~
~~-pyrrolyl,~~
~~-oxadiazolyl,~~
~~-thiadiazolyl,~~
~~-triazolyl,~~
~~-tetrazolyl,~~
~~-oxazolopyridinyl,~~
~~-imidazopyridinyl,~~
~~-isothiazolyl,~~
~~-naphthyridinyl,~~
~~-cinnolinyl,~~
~~-carbazolyl,~~
~~-beta-carbolinyl,~~
~~-isochromanyl,~~
~~-chromanyl,~~
~~-tetrahydroisoquinolinyl,~~
~~-isoindolinyl,~~
~~-isobenzotetrahydrofuranyl,~~
~~-isobenzotetrahydrothienyl,~~
~~-isobenzothienyl,~~
~~-benzoxazolyl,~~
~~-pyridopyridinyl,~~

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~~-benzotetrahydrofuranyl,~~
~~-benzotetrahydrothienyl,~~
~~-purinyl,~~
~~-benzodioxolyl,~~
~~-triazinyl,~~
~~-benoxazinyl,~~
~~-phenothiazinyl,~~
~~-pteridinyl,~~
~~-benzothiazolyl,~~
~~-imidazopyridinyl,~~
~~-imidazothiazolyl,~~
~~-dihydrobenzisoxazinyl,~~
~~-benzisoxazinyl,~~
~~-benzoxazinyl,~~
~~-dihydrobenzisothiazinyl,~~
~~-benzopyranyl,~~
~~-benzothiopyranyl,~~
~~-coumarinyl,~~
~~-isocoumarinyl,~~
~~-chromonyl,~~
~~-chromanonyl,~~
~~-pyridinyl-N-oxide,~~
~~tetrahydroquinolinyl~~
~~dihydroquinolinyl~~
~~dihydroquinolinonyl~~
~~dihydroisoquinolinonyl~~
~~dihydrocoumarinyl~~
~~dihydroisocoumarinyl~~
~~isoindolinonyl~~
~~benzodioxanyl~~
~~benzoxazolinonyl~~
~~pyrrolyl-N-oxide,~~

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~~pyrimidinyl N-oxide,~~
~~pyridazinyl N-oxide,~~
~~pyrazinyl N-oxide,~~
~~quinolinyl N-oxide,~~
~~indolyl N-oxide,~~
~~indolinyl N-oxide,~~
~~isoquinolyl N-oxide,~~
~~quinazolinyl N-oxide,~~
~~quinoxalinyl N-oxide,~~
~~phthalazinyl N-oxide,~~
~~imidazolyl N-oxide,~~
~~isoxazolyl N-oxide,~~
~~oxazolyl N-oxide,~~
~~thiazolyl N-oxide,~~
~~indolizinyl N-oxide,~~
~~indazolyl N-oxide,~~
~~benzothiazolyl N-oxide,~~
~~benzimidazolyl N-oxide,~~
~~pyrrolyl N-oxide,~~
~~oxadiazolyl N-oxide,~~
~~thiadiazolyl N-oxide,~~
~~triazolyl N-oxide,~~
~~tetrazolyl N-oxide,~~
~~benzothiopyranyl S-oxide, and~~
~~benzothiopyranyl S,S-dioxide,~~

~~where the $R_{N\text{-heteroaryl}}$ group is bonded by any atom of the parent $R_{N\text{-heteroaryl}}$ group substituted by hydrogen such that the new bond to the $R_{N\text{-heteroaryl}}$ group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:~~

~~(1) C_1-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group~~

~~consisting of C_1-C_3 alkyl, F, Cl, Br, I, OH, SH, C≡N, CF_3, C_1-C_3 alkoxy, and $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,~~

~~(2) OH,~~

~~(3) NO_2,~~

~~(4) F, Cl, Br, I,~~

~~(5) CO-OH,~~

~~(6) C≡N,~~

~~(7) $-(CH_2)_{0-4}$-CO-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are the same or different and are selected from the group consisting of:~~

~~(a) H,~~

~~(b) C_1-C_6 alkyl optionally substituted with one substitutent selected from the group consisting of:~~

~~(i) OH, and~~

~~(ii) NH_2,~~

~~(c) C_1-C_6 alkyl optionally substituted with one to three F, Cl, Br, I,~~

~~(d) C_3-C_7 cycloalkyl,~~

~~(e) $-(C_1$-C_3 alkyl)-(C_3-C_7 cycloalkyl),~~

~~(f) (C_1-C_6 alkyl)-O-(C_1-C_3 alkyl),~~

~~(g) C_2-C_6 alkenyl with one or two double bonds,~~

~~(h) C_2-C_6 alkynyl with one or two triple bonds,~~

~~(i) C_1-C_6 alkyl chain with one double bond and one triple bond,~~

~~(j) R_{1-aryl} where R_{1-aryl} is as defined above, and~~

~~(k) $R_{1-heteroaryl}$ where $R_{1-heteroaryl}$ is as defined above,~~

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(8) $(CH_2)_{0-4}$-CO-(C_1-C_{12} alkyl),

(9) $(CH_2)_{0-4}$-CO-(C_2-C_{12} alkenyl with one, two or three double bonds),

(10) $(CH_2)_{0-4}$-CO-(C_2-C_{12} alkynyl with one, two or three triple bonds),

(11) $(CH_2)_{0-4}$-CO-(C_3-C_7 cycloalkyl),

(12) $(CH_2)_{0-4}$-CO-$R_{1\text{-aryl}}$ where $R_{1\text{-aryl}}$ is as defined above,

(13) $(CH_2)_{0-4}$-CO-$R_{1\text{-heteroaryl}}$ where $R_{1\text{-heteroaryl}}$ is as defined above,

(14) $(CH_2)_{0-4}$-CO-$R_{1\text{-heterocycle}}$ where $R_{1\text{-heterocycle}}$ is as defined above,

(15) $(CH_2)_{0-4}$-CO-R_{N-4} where R_{N-4} is selected from the group consisting of morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl where each group is optionally substituted with one, two, three, or four of C_1-C_6 alkyl,

(16) $(CH_2)_{0-4}$-CO-O-R_{N-5} where R_{N-5} is selected from the group consisting of:

(a) C_1-C_6 alkyl,

(b) $(CH_2)_{0-2}$-($R_{1\text{-aryl}}$) where $R_{1\text{-aryl}}$ is as defined above,

(c) C_2-C_6 alkenyl containing one or two double bonds,

(d) C_2-C_6 alkynyl containing one or two triple bonds,

(e) C_3-C_7 cycloalkyl, and

(f) $(CH_2)_{0-2}$-($R_{1\text{-heteroaryl}}$) where $R_{1\text{-heteroaryl}}$ is as defined above,

(17) $(CH_2)_{0-4}$-SO_2-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} are as defined above,

(18) $(CH_2)_{0-4}$-SO-(C_1-C_8 alkyl),

(19) $(CH_2)_{0-4}$-SO_2-(C_2-C_{10} alkyl),

(20) $(CH_2)_{0-4}$-SO_2-(C_3-C_7 cycloalkyl),

(21) $(CH_2)_{0-4}$-N(H or R_{N-5})-CO-O-R_{N-5} where R_{N-5} can be the same or different and is as defined above,

(22) $(CH_2)_{0-4}$-N(H or R_{N-5})-CO-$N(R_{N-5})_2$, where R_{N-5} can be the same or different and is as defined above,

(23) $(CH_2)_{0-4}$-N-CS-$N(R_{N-5})_2$, where R_{N-5} can be the same or different and is as defined above,

(24) $(CH_2)_{0-4}$-N(-H or R_{N-5})-CO-R_{N-2} where R_{N-5} and R_{N-2} can be the same or different and are as defined above,

(25) $(CH_2)_{0-4}$-$NR_{N-2}R_{N-3}$ where R_{N-2} and R_{N-3} can be the same or different and are as defined above,

(26) $(CH_2)_{0-4}$-R_{N-4} where R_{N-4} is as defined above,

(27) $(CH_2)_{0-4}$-O-CO-(C_1-C_6 alkyl),

(28) $(CH_2)_{0-4}$-O-P(O)-$(OR_{N\ aryl-1})_2$ where $R_{N\ aryl-1}$ is H or C_1-C_4 alkyl,

(29) $(CH_2)_{0-4}$-O-CO-$N(R_{N-5})_2$ where R_{N-5} is as defined above,

(30) $(CH_2)_{0-4}$-O-CS-$N(R_{N-5})_2$ where R_{N-5} is as defined above,

(31) $(CH_2)_{0-4}$-O-$(R_{N-5})_2$ where R_{N-5} is as defined above,

(32) $(CH_2)_{0-4}$-O-(R_{N-5})-COOH where R_{N-5} is as defined above,

(33) $(CH_2)_{0-4}$-S-(R_{N-5}) where R_{N-5} is as defined above,

(34) $(CH_2)_{0-4}$-O-(C_1-C_6 alkyl optionally substituted with one, two, three, four, or five of F),

(35) C_3-C_7 cycloalkyl,

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~~(36) C_2-C_6 alkenyl with one or two double bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\_a}R_{1\_b}$ where R_{1_a} and R_{1_b} are as defined above,~~

~~(37) C_2-C_6 alkynyl with one or two triple bonds optionally substituted with C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_3 alkoxy, and $-NR_{1\_a}R_{1\_b}$ where R_{1_a} and R_{1_b} are as defined above,~~

~~(38) $-(CH_2)_{0-4}N(H \text{ or } R_{N\_5})SO_2R_{N\_6}$ where R_{N_6} and R_{N_2} can be the same or different and are as described above, or~~

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~~(39) $-(CH_2)_{0-4}$-C_3-C_4 cycloalkyl,~~

~~(C) $R_{N\text{-}aryl}$-W-$R_{N\text{-}aryl}$,~~

~~(D) $R_{N\text{-}aryl}$-W-$R_{N\text{-}heteroaryl}$,~~

~~(E) $R_{N\text{-}aryl}$-W-$R_{N\text{-}1\ heterocycle}$, where $R_{N\ heterocycle}$ is the same as $R_{1\ heterocycle}$~~

~~(F) $R_{N\ heteroaryl}$-W-$R_{N\text{-}aryl}$,~~

~~(G) $R_{N\ heteroaryl}$-W-$R_{N\text{-}heteroaryl}$,~~

~~(H) $R_{N\ heteroaryl}$-W-$R_{N\text{-}1\ heterocycle}$, where $R_{N\text{-}1\ heterocycle}$ is the same as $R_{1\ heterocycle}$,~~

~~(I) $R_{N\ heterocycle}$-W-$R_{N\text{-}aryl}$,~~

~~(J) $R_{N\text{-}heterocycle}$-W-$R_{N\ heteroaryl}$,~~

~~(K) $R_{N\ heterocycle}$-W-$R_{N\text{-}1\text{-}heterocycle}$,~~

~~where W is~~

~~(1) $-(CH_2)_{0-4}$-,~~

~~(2) -O-,~~

~~(3) $-C(O)_{0-2}$-,~~

~~(4) $-N(R_{N\_5})$ where R_{N_5} is as defined above, or~~

~~(5) -CO-,~~

where R_C is:

(I) -C_3-C_{10} alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -$NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, -OC=O $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, -$S(=O)_{0-2}$ R_{1-a} where R_{1-a} is as defined above, -NR_{1-a}C=O $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, -C=O $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above, and -$S(=O)_2$ $NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(II) -$(CH_2)_{0-3}$-(C_3-C_8) cycloalkyl where cycloalkyl can be optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF_3, C_1-C_6 alkoxy, -O-phenyl, -CO-OH, -CO-O-(C_1-C_4 alkyl), and -$NR_{1-a}R_{1-b}$ where R_{1-a} and R_{1-b} are as defined above,

(III) -$(CR_{C-x}R_{C-y})_{0-4}$-R_{C-aryl} where R_{C-x} and R_{C-y} are

-H,

C_1-C_4 alkyl optionally substituted with one or two -OH,

C_1-C_4 alkoxy optionally substituted with one, two, or three of -F,

-$(CH_2)_{0-4}$-C_3-C_7 cycloalkyl,

C_2-C_6 alkenyl containing one or two double bonds,

C_2-C_6 alkynyl containing one or two triple bonds, or

phenyl,

and where R_{C-x} and R_{C-y} are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six or seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, $-SO_2-$, $-NR_{N-2}-$ and R_{C-aryl} is the same as R_{N-aryl};

(IV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$ is the same as $R_{N-heteroaryl}$ and R_{C-x} and R_{C-y} are as defined above,

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(V) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-aryl}$ where R_{C-aryl}, R_{C-x} and R_{C-y} are as defined above,

(VI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heteroaryl}$ where R_{C-aryl}, $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(VII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-aryl}$ where $R_{C-heteroaryl}$, R_{C-aryl}, R_{C-x} and R_{C-y} are as defined above,

(VIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heteroaryl}$ where $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(IX) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heterocycle}$ where R_{C-aryl}, R_{C-x} and R_{C-y} are as defined above, and $R_{C-heterocycle}$ is the same as $R_{N-heterocycle}$,

(X) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-heterocycle}$ where $R_{C-heteroaryl}$, $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XI) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-aryl}$ where $R_{C-heterocycle}$, R_{C-aryl}, R_{C-x} and R_{C-y} are as defined above,

(XII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heteroaryl}$ where $R_{C-heterocycle}$, $R_{C-heteroaryl}$, R_{C-x} and R_{C-y} are as defined above,

(XIII) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XIV) $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}$ where $R_{C-heterocycle}$, R_{C-x} and R_{C-y} are as defined above,

(XV) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring fused to $R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$ or $R_{C\text{-}heterocycle}$ where $R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$ or $R_{C\text{-}heterocycle}$ are as defined above where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally replaced with NH, $NR_{N\text{-}5}$, O, $S(=O)_{0\text{-}2}$, and where cyclopentyl, cyclohexyl, or -cycloheptyl can be optionally substituted with one or two $-C_1$-C_3 alkyl, -F, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, =O, or $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(XVI) $-[C(R_{C\text{-}1})(R_{C\text{-}2})]_{1\text{-}3}$-CO-N-$(R_{C\text{-}3})_2$ where $R_{C\text{-}1}$ and $R_{C\text{-}2}$ are the same or different and are selected from the group consisting of:

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(A) -H,

(B) $-C_1$-C_6 alkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(C) C_2-C_6 alkenyl with one or two double bonds, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(C) $-(CH_2)_{0\text{-}4}$-C_3-C_7 cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(D) $-(C_1$-C_4 alkyl$)$-$R_{C'\text{-}aryl}$ where $R_{C'\text{-}aryl}$ is as defined for $R_{1\text{-}aryl}$,

(E) $-(C_1$-C_4 alkyl$)$-$R_{C\text{-}heteroaryl}$ where $R_{C\text{-}heteroaryl}$ is as defined above,

(F) $-(C_1-C_4$ alkyl$)-R_{C\text{-}heterocycle}$ where $R_{C\text{-}heterocycle}$ is as defined above,

(G) $-R_{C\text{-}heteroaryl}$ where $R_{C\text{-}heteroaryl}$ is as defined above,

(H) $-R_{C\text{-}heterocycle}$ where $R_{C\text{-}heterocycle}$ is as defined above, and

(I) $-R_{C'\text{-}aryl}$ where $R_{C'\text{-}aryl}$ is as defined above,

and where $R_{C\text{-}3}$ is the same or different and is:

(A) -H,

(B) $-C_1-C_6$ alkyl optionally substituted with one, two or three substituents selected from the group consisting of C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, $-CF_3$, C_1-C_6 alkoxy, -O-phenyl, and $-NR_{1\text{-}a}R_{1\text{-}b}$ where $R_{1\text{-}a}$ and $R_{1\text{-}b}$ are as defined above,

(C) $-(CH_2)_{0\text{-}4}-C_3-C_7$ cycloalkyl,

(D) $-(C_1-C_4$ alkyl$)-R_{C'\text{-}aryl}$ where $R_{C'\text{-}aryl}$ is as defined above,

(E) $-(C_1-C_4$ alkyl$)-R_{C\text{-}heteroaryl}$ where $R_{C\text{-}heteroaryl}$ is as defined above, or

(F) $-(C_1-C_4$ alkyl$)-R_{C\text{-}heterocycle}$ where $R_{C\text{-}heterocycle}$ is as defined above; or

pharmaceutically acceptable salts thereof.

2. (Currently Amended) A substituted amine according to claim 1

where ~~R_1 is:~~

~~$(CH_2)_{0\text{-}2}-(R_{1\text{-}aryl})$, or~~

~~$(CH_2)_{0\text{-}1}-(R_{1\text{-}heteroaryl})$~~

~~where R_N is:~~

~~R_{N-1}-X_N where X_N is selected from the group consisting of:~~

~~-CO-, and~~

~~-SO_2-,~~

~~where R_{N-1} is selected from the group consisting of:~~

~~$R_{N\text{-}aryl}$, and~~

~~$R_{N\text{-}heteroaryl}$~~

where R_C is:

$-C_3$-C_8 alkyl,

$-(CH_2)_{0-3}-(C_3-C_7)$ cycloalkyl,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}aryl}$,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}heteroaryl}$,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}heterocycle}$, or

-cyclopentyl or -cyclohexyl ring fused to $R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$ or $R_{C\text{-}heterocycle}$.

3. (Currently Amended) A substituted amine according to claim 2

where R_1 is:

$-(CH_2)-(R_{1\text{-}aryl})$, ~~or~~

~~$(CH_2)-(R_{1\text{-}heteroaryl})$,~~

where R_2 is -H;

where R_3 is -H;

~~where R_N is:~~

~~R_{N-1}-X_N where X_N is:~~

~~-CO-,~~

~~where R_{N-1} is selected from the group consisting of:~~

~~$R_{N\text{-}aryl}$, and~~

~~$R_{N\text{-}heteroaryl}$~~

where R_C is:

$-(CH_2)_{0-3}-(C_3-C_7)$ cycloalkyl,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C-aryl}$,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C-heteroaryl}$,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C-heterocycle}$, or

-cyclopentyl or -cyclohexyl ring fused to a R_{C-aryl} or $R_{C-heteroaryl}$ or $R_{C-heterocycle}$.

4. (Original) A substituted amine according to claim 3 where R_C is:

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$-(CR_{C-x}R_{C-y})_{1-4}-R_{C-aryl}$,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C-heteroaryl}$,, or

-cyclopentyl or -cyclohexyl ring fused to a R_{C-aryl} or $R_{C-heteroaryl}$ or $R_{C-heterocycle}$.

5. (Cancelled)

6. (Original) A substituted amine according to claim 1 where R_1 is

$-(CH_2)-(R_{1-aryl})$ where R_{1-aryl} is phenyl substituted with two -F.

7. (Original) A substituted amine according to claim 6 where the -F substitution is 3,5-difluorobenzyl.

8. (Original) A substituted amine according to claim 1 where R_2 is -H.

9. (Original) A substituted amine according to claim 1 where R_3 is -H.

10. (Currently Amended) A substituted amine according to claim 1 where ~~R_N is R_{N-1}-X_N- where X_N is CO, where R_{N-1} is $R_{N\text{-}aryl}$ where~~ $R_{N\text{-}aryl}$ is phenyl substituted with one $-CO-NR_{N-2}R_{N-3}$ where the substitution on the phenyl is 1,3-.

11. (Original) A substituted amine according to claim 10 where R_{N-2} and R_{N-3} are the same and are C_3 alkyl.

12. (Currently Amended) A substituted amine according to claim 1 where R_N is ~~R_{N-1}-X_N- where X_N is CO, where R_{N-1} is $R_{N\text{-}aryl}$~~ where $R_{N\text{-}aryl}$ is phenyl substituted with one C_1 alkyl and with one $-CO-NR_{N-2}R_{N-3}$ where the substitution on the phenyl is 1,3,5-.

13. (Original) A substituted amine according to claim 12 where R_{N-2} and R_{N-3} are the same and are C_3 alkyl.

14. (Cancelled)

15. (Cancelled)

16. (Original) A substituted amine according to claim 1 where R_C is:

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}aryl}$ where $R_{C\text{-}aryl}$ is phenyl,

$-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}heteroaryl}$, or

-cyclopentyl or -cyclohexyl ring fused to a $R_{C\text{-}aryl}$ or $R_{C\text{-}heteroaryl}$ or $R_{C\text{-}heterocycle}$.

17. (Original) A substituted amine according to claim 16 where R_C is: $-(CR_{C-x}R_{C-y})_{1-4}-R_{C\text{-}aryl}$ where $R_{C\text{-}aryl}$ is phenyl.

18. (Original) A substituted amine according to claim 17 where phenyl is substituted in the 3-position or 3,5-positions.

19. (Original) A substituted amine according to claim 16 where R_C is:

$-(CH_2)-R_{C\text{-}heteroaryl}$.

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20. (Original) A substituted amine according to claim 16 where R_C is:

$-(CH_2)-R_{C\text{-}heterocycle}$.

21. (Original) A substituted amine according to claim 16 where R_C is:

-cyclohexyl ring fused to a phenyl ring.

22. (Original) A substituted amine according to claim 1 where the pharmaceutically acceptable salt is selected from the group consisting of salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric,

dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic.

23. (Original) A substituted amine according to claim 1 which is selected from
the group consisting of:

N^1-[(1S,2S)-1-(3,5-difluorobenzyl)-3-(hexylamino)-2-hydroxypropyl]-N^3,N^3-dipropylisophthalamide,

N^1-[(1S,2S)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide,

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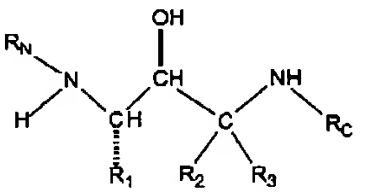
N^1-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide, and

N^1-(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-(isobutylamino)-1-methyl-2-oxoethyl]amino}propyl)-N^3,N^3-dipropylisophthalamide.

24. (Original) A method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's

disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound selected from the group consisting of a substituted amine of formula (X)



(X)

A1

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, and pharmaceutically acceptable salts thereof.

25. (Original) A method of treatment according to claim 24 where the disease is Alzheimer's disease.

26. (Original) A method of treatment according to claim 24 where the method is helping prevent or delay the onset of Alzheimer's disease.

27. (Original) A method of treatment according to claim 24 where the disease is mild cognitive impairment.

28. (Original) A method of treatment according to claim 24 where the disease is Down's syndrome.

29. (Original) A method of treatment according to claim 24 where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

30. (Original) A method of treatment according to claim 24 where the disease is cerebral amyloid angiopathy.

31. (Original) A method of treatment according to claim 24 where the disease is degenerative dementias.

32. (Original) A method of treatment according to claim 24 where the disease is diffuse Lewy body type of Alzheimer's disease.

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33. (Original) A method of treatment according to claim 24 where the method is treating an existing disease.

34. (Original) A method of treatment according to claim 24 where the method is preventing a disease from developing.

35. (Original) A method of treatment according to claim 24 where the therapeutically effective amount for oral administration is from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration is from about 0.5 to about 100 mg/day; for depo administration and implants is from about 0.5 mg/day to about 50 mg/day; for topical administration is from about 0.5 mg/day to about 200 mg/day; for rectal administration is from about 0.5 mg to about 500 mg.

36. (Original) A method of treatment according to claim 35 where the therapeutically effective amount is for oral administration is from about 1 mg/day to about 100 mg/day and for parenteral administration is from about 5 to about 50 mg daily.

37. (Original) A method of treatment according to claim 36 where the therapeutically effective amount for oral administration is from about 5 mg/day to about 50 mg/day.

38. (Original) A method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound selected from the group consisting of:

N^1-[(1S,2S)-1-(3,5-difluorobenzyl)-3-(hexylamino)-2-hydroxypropyl]-N^3,N^3-dipropylisophthalamide,

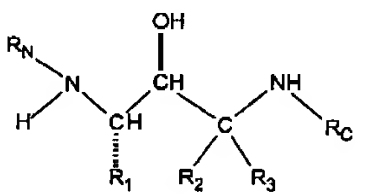
N^1-[(1S,2S)-3-(benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N^3,N^3-dipropylisophthalamide,

N^1-{(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-methyl-N^3,N^3-dipropylisophthalamide, and

N^1-(1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-(isobutylamino)-1- methyl-2-oxoethyl]amino}propyl)- N^3,N^3-dipropylisophthalamide; and

a pharmaceutically acceptable salt thereof.

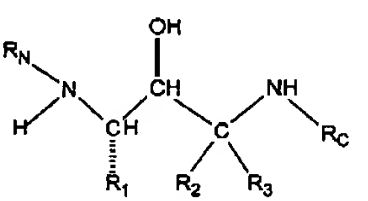
39. (Original) A pharmaceutical composition which comprises a substituted amine of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

40. (Original) A method for inhibiting beta-secretase activity, comprising exposing said beta-secretase to an effective inhibitory amount of a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

41. (Original) The method of claim 40, wherein said beta-secretase is exposed to said compound *in vitro*.

42. (Original) The method of claim 40, wherein said beta-secretase is exposed to said compound in a cell.

43. (Original) The method of claim 42, wherein said cell is in an animal.

44. (Original) The method of claim 43, wherein said animal is a human.

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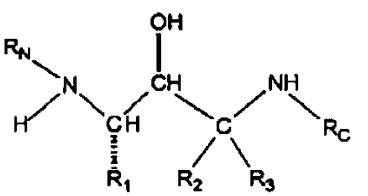
45. (Original) A method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, comprising exposing said reaction mixture to an effective inhibitory amount of a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

46. (Original) The method of claim 45, wherein said cleavage site is between Met652 and Asp653, numbered for the APP-751 isotype; between Met 671 and Asp 672, numbered for the

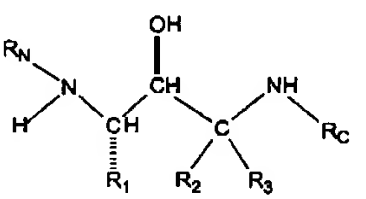
APP-770 isotype; between Leu596 and Asp597 of the APP-695 Swedish Mutation; between Leu652 and Asp653 of the APP-751 Swedish Mutation; or between Leu671 and Asp672 of the APP-770 Swedish Mutation.

47. (Original) The method of claim 45, wherein said reaction mixture is exposed *in vitro*.

48. (Original) The method of claim 47, wherein said reaction mixture is exposed in a cell.

49. (Original) The method of claim 48, wherein said cell is a human cell.

50. (Original) A method for inhibiting production of amyloid beta peptide (A beta) in a cell, comprising administering to said cell an effective inhibitory amount of a compound of formula (X)



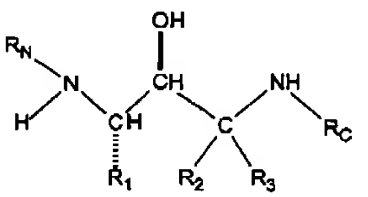
(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

51. (Original) The method of claim 50, wherein said administering is to an animal.

52. (Original) The method of claim 51, wherein said administering is to a human.

53. (Original) A method for inhibiting the production of beta-amyloid plaque in an animal, comprising administering to said animal an effective inhibitory amount of a compound of formula (X)

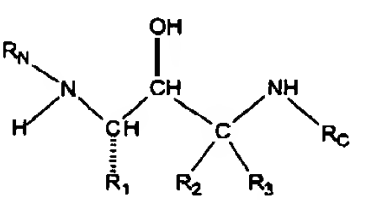


(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

54. (Original) The method of claim 53, wherein said animal is a human.

55. (Original) A method for treating or preventing a disease characterized by beta-amyloid deposits in the brain comprising administering to a patient an effective therapeutic amount of a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

56. (Original) The method of claim 55, wherein said therapeutic amount is in the range of from about 0.1 to about 1000 mg/day.

57. (Currently Amended) The method of claim 55, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 15 to about 1500 mg/day.

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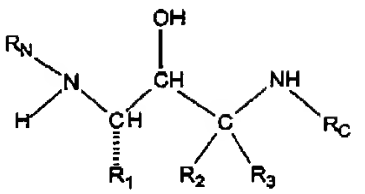
58. (Currently Amended) The method of claim 57, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 1 to about 100 mg/day.

59. (Currently Amended) The method of claim 58, wherein said ~~therapeutic~~ therapeutic amount is in the range of from about 5 to about 50 mg/day.

60. (Original) The method of claim 55, wherein said disease is Alzheimer's disease.

61. (Original) The method of claim 55, wherein said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemmorrhage with Amyloidosis of the Dutch Type.

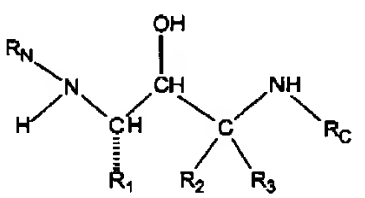
62. (Original) A composition comprising beta-secretase complexed with a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

63. (Original) A method for producing a beta-secretase complex comprising: exposing beta-secretase, in a reaction mixture under conditions suitable for the production of said complex, to a compound of formula (X)



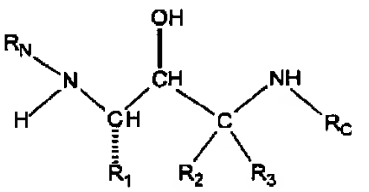
(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

64. (Original) The method of claim 63, where said exposing is *in vitro*.

65. (Original) The method of claim 63, wherein said reaction mixture is a cell.

66. (Original) A kit comprising component parts capable of being assembled, wherein at least one component part comprises, enclosed in a container, a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

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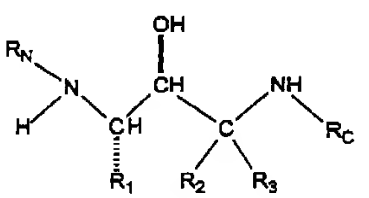
67. (Original) The kit of claim 66, wherein said compound is lyophilized and at least one further component part comprises a diluent.

68. (Original) A kit comprising a plurality of containers, each container comprising one or more unit dose of a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

69. (Original) The kit of claim 68, wherein each container is adapted for oral delivery and comprises a tablet, gel, or capsule.

70. (Currently Amended) The kit of claim 69, wherein each container is adapted for ~~parenternal~~ parenteral delivery and comprises a depot product, syringe, ampoule, or vial.

71. (Original) The kit of claim 69, wherein each container is adapted for topical delivery and comprises a patch, medipad, ointment, or cream.

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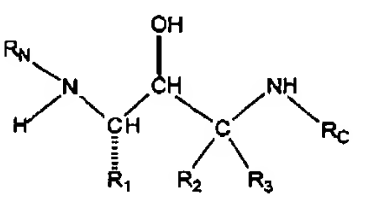
72. (Currently Amended) A kit comprising one or more therapeutic agent selected from the group consisting of an antioxidant, an ~~anti-inflamatory,~~ anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetylcholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody; and

a compound of formula (X)

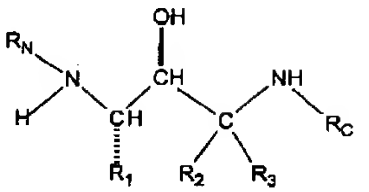


(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

73. (Original) A composition comprising an inert diluent or edible carrier; and

a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof.

74. (Original) The composition of claim 73, wherein said carrier is an oil.

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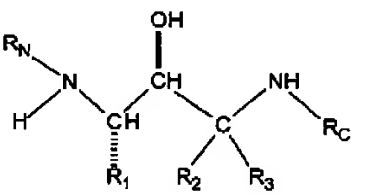
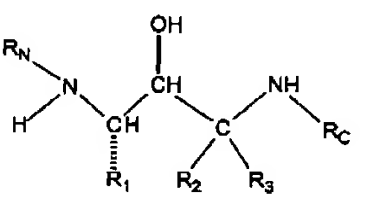
75. (Original) A composition comprising a binder, excipient, disintegrating agent, lubricant, or gildant; and a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof..

76. (Original) A composition comprising a compound of formula (X)



(X)

where R_1, R_2, R_3, R_N and R_C are as defined in claim 1, or a pharmaceutically acceptable salt thereof, and where the compound is disposed in a cream, ointment, or patch.

A1